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(54) **The preparation of n-acyl-alpha-amino acids**

(57) A process for the preparation of N-acyl- α -amino acids by reacting carbon monoxide with an aldehyde and a carboxylic acid amide having an amide group with at least one hydrogen atom attached to the nitrogen atom which reaction is carried out in the presence of a catalyst, obtainable from a compound containing a metal selected from the iron group of the Periodic Table, and a cocatalyst which is an acid with a pKa of less than 3 added in a quantity of less than 0.1 mol per mol of the carboxylic acid amide.

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PROCESS FOR THE PREPARATION OF N-ACYL- α -AMINO ACIDS

The invention relates to a process for the preparation of N-acyl- α -amino acids.

N-acyl- α -amino acids are possible intermediates for the production of, for example, pharmaceuticals and food additives, such as sweeteners. The availability of a simple process for their synthesis from readily available feedstock is therefore of high importance. One such process involves the reaction of carbon monoxide with an aldehyde and a carboxylic acid amide catalysed by an iron group metal, in particular cobalt, which reaction is known, inter alia, from US-A-3766266 and from J.-J. Parnaud et al., Journal of Molecular Catalysis, 6 (1979) pp. 341 - 350. The present invention aims at improving the latter process, in particular, with respect to the rate of reaction.

One improvement of said process for the preparation of N-acyl- α -amino acids is known from EP-A-197659. Herein, carbon monoxide is reacted with an aldehyde and a carboxylic acid amide having an amide group with at least one hydrogen atom attached to the nitrogen atom which reaction is carried out in the presence of a catalyst, obtainable from a compound containing a metal selected from the iron group of the Periodic Table, and a cocatalyst which contains a nitrile or a tertiary phosphine. In this process the function of the cocatalyst is, a.o., to increase the selectivity of the reaction to the desired N-acyl- α -amino acid by preventing the formation of an N,N'-diacyl-1,1-diaminoalkane. However, the reaction rate leaves room for improvement, irrespective of whether or not the reaction is being carried out in the presence of said cocatalysts.

It has now been found that the use of a strong acid, i.e. an acid with a pKa of less than 3, as a cocatalyst in the reaction of

carbon monoxide with an aldehyde and a carboxylic acid amide catalysed by an iron group metal leads to a considerably increased rate of formation of the N-acyl- α -amino acids.

Accordingly, the present invention relates to a process for
5 the preparation of N-acyl- α -amino acids by reacting carbon monoxide with an aldehyde and a carboxylic acid amide having an amide group with at least one hydrogen atom attached to the nitrogen atom which reaction is carried out in the presence of a catalyst, obtainable
10 from a compound containing a metal selected from the iron group of the Periodic Table, and a cocatalyst which is an acid with a pKa of less than 3 added in a quantity of less than 0.1 mol per mol of the carboxylic acid amide.

The invention also relates to N-acyl- α -amino acids obtained by the process of the invention.

15 Provided the quantity of the strong acid is kept low, the reaction of the process of the invention proceeds without appreciable formation of by-products. The present finding is surprising in view of US-A-3766266 wherein it is disclosed that the reaction of carbon monoxide with acetaldehyde and acetamide in the
20 presence of a large quantity of hydrochloric acid proceeds with a very low yield of N-acylalanine. In this reaction a stoichiometric quantity of dicobalt octacarbonyl is used as the source of carbon monoxide.

The process, indicated hereinbefore, in which a nitrile or a
25 tertiary phosphine is used as a cocatalyst, requires the presence of hydrogen, suitably at a partial pressure of several tens of bars, to achieve the maximum catalyst activity. Unexpectedly, it has now been found that in the present process, carried out with a strong acid as cocatalyst, high reaction rates can be achieved
30 without having hydrogen present. Thus, in the present process the presence of hydrogen is superfluous. This will imply a simplification of the process when it is carried out at a commercial scale, because, e.g., a significantly lower total pressure can be applied and the recycle of gaseous streams may be
35 much easier.

The acid used in the process of the invention must be a strong acid, i.e. an acid with a pKa of less than 3, the pKa being measured in water at 25 °C. Preferably the pKa of the acid is less than 2. The acid may be inorganic as well as organic. Although
5 the acid may be bound to a high-molecular weight matrix, e.g. a polymeric carrier, it is preferred to use an acid having a low molecular weight. Thus, in case of an organic acid, the acid may contain up to 20 carbon atoms, in particular up to 10 carbon atoms. Preferably, the cocatalyst is an acid selected from the group
10 consisting of sulphonic acids, carboxylic acids, phosphonic acids and hydrohalogenic acids. Examples of such acids are trifluoromethanesulphonic acid, α -naphthalenesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, trifluoroacetic acid, di- and trichloroacetic acid, pentafluoropropionic acid,
15 α -naphthalenephosphonic acid, benzenephosphonic acid, hydrochloric acid and hydrobromic acid. Particularly preferred are (perfluoro-n-alkyl)sulphonic acids. Very good results can be obtained with trifluoromethanesulphonic acid, p-toluenesulphonic acid, trifluoroacetic acid, benzenephosphonic acid and hydrochloric
20 acid, especially with trifluoromethanesulphonic acid.

In order to prevent the formation of by-products, the cocatalyst of the invention is present in a quantity of less than 0.1 mol per mol of the carboxylic acid amide. Preferably, the cocatalyst is present in a quantity of from 0.0001 to 0.05 mol, in
25 particular from 0.001 to 0.03 mol, per mol of the carboxylic acid amide. It is furthermore preferred not to use the cocatalyst in a large excess over the catalyst. Thus, the cocatalyst is suitably present in a quantity of from 0.1 to 2 mol, especially from 0.5 to 1 mol, per gram atom of the iron group metal present in the
30 catalyst. It is not important in which quantity the cocatalyst is present relative to the quantity of aldehyde. Suitably, the cocatalyst is present in a quantity of less than 0.1 mol per mol of aldehyde, preferably in a quantity of from 0.0001 to 0.05 mol and in particular from 0.001 to 0.03 mol per mol of the aldehyde.

The catalyst in the process of the invention is obtainable from a compound which contains a metal of the iron group of the Periodic Table. The iron group consists of the metals iron, cobalt and nickel, of which cobalt is the preferred metal.

5 The catalyst of which the iron group metal is cobalt may be obtained from various types of cobalt containing compounds. Eligible are compounds which comprise zero-valent cobalt, such as finely dispersed supported metallic cobalt, organic and inorganic salts, for example, halides, such as cobalt chloride and cobalt
10 bromide, aromatic and aliphatic carboxylates, such as cobalt acetate, cobalt stearate and cobalt naphthenate, and complex compounds containing one or more ligands, such as nitriles and phosphines. The ligands may also be added to the reaction mixture separately from the cobalt containing compounds. The preferred
15 cobalt containing compounds are cobalt carbonyls, for example compounds of the formulae $\text{Co}_2(\text{CO})_8$, $\text{Co}_4(\text{CO})_{12}$ and $\text{HCo}(\text{CO})_3$. Very good results can be achieved with dicobalt octacarbonyl, $\text{Co}_2(\text{CO})_8$.

A skilled person will appreciate that the catalyst is used in a catalytic quantity, i.e. the molar ratios of the quantity of the
20 iron group metal present in the catalyst to the quantities of each of the reactants, the aldehyde and the carboxylic acid amide, is less than one. The catalyst is suitably present in such a quantity as to contain from 0.0001 to 0.05 gram atom iron group metal, in particular from 0.001 to 0.03 gram atom iron group metal, per mol
25 of the carboxylic acid amide.

Various aldehydes can be used in the process of the invention. The aldehydes may comprise more than one formyl group and besides the oxygen atom(s) of the formyl group(s) the aldehyde may contain other oxygen atoms or other heteroatoms, such as in, for example,
30 (3-N-acylindolyl)acetaldehyde, 4-acetoxyphenylacetaldehyde, β -methylmercaptopropionaldehyde and β -formylpropionic acid. Suitably, the aldehyde is of the general formula R-CHO wherein R represents hydrogen or a hydrocarbyl group, such as a (cyclo)alkyl, an arylalkyl or an (alkyl)aryl group, suitably, containing up to 20
35 carbon atoms, more suitably up to 10 carbon atoms. Examples of

such aldehydes are phenylacetaldehyde, formylcyclohexane and 4-methylbenzaldehyde. Preferably, R represents hydrogen or an alkyl group, such as in, for example, formaldehyde, acetaldehyde and isobutyraldehyde.

5 Various carboxylic acid amides having an amide group with at least one hydrogen atom attached to the nitrogen atom can be used in the process of the invention. The carboxylic acid amides may comprise more than one carboxylic acid amide group and include primary and secondary carboxylic acid amides. Examples of such
10 carboxylic acid amides are N-acetylmethionine amide, pyrrolidone carboxylic acid amide, N-ethylacetamide and acid amide derivatives of aspartic acid. Suitably, the carboxylic acid amide is of the general formula $R^1\text{-CO-NH-R}^2$, wherein R^1 and R^2 represent independently hydrogen or a hydrocarbyl group, such as a
15 (cyclo)alkyl, an arylalkyl or an (alkyl)aryl group, for example N-hexadecylformamide, (4-dodecylphenyl)acetamide and N-methyladamantylacetamide. Suitably, the hydrocarbyl groups of R^1 and R^2 contain up to 20 carbon atoms, more suitably up to 10 carbon atoms. Preferably, R^1 represents an alkyl group, in particular a
20 n-alkyl group, suitably, containing up to 4 carbon atoms. R^2 represents preferably hydrogen or an alkyl group. Especially preferred carboxylic acid amides are the primary amides, so that R^2 more preferably represents hydrogen.

 In the process of the invention the carboxylic acid amide and
25 the aldehyde may be added as such or they may be formed in situ from eligible precursors in a preliminary reaction or simultaneously with the formation of the N-acetyl- α -amino acid. For example, the aldehyde may be formed from an olefin, carbon monoxide and hydrogen by hydroformylation, from an epoxide by
30 isomerisation or from a polymeric form of the aldehyde by depolymerisation.

 The carbonyl group(s) of the aldehyde and the amide group(s) of the carboxylic acid amide may be present in one compound, so that a cyclic N-acyl- α -amino acid can be formed.
35 β -Formylpropionamide is an example of such a starting material.

It is not important at which molar ratio the carboxylic acid amide and the aldehyde are brought together in the reaction mixture of the process of the invention. Suitably the aldehyde is used in a quantity of from 0.1 to 10 mol, more suitably from 0.3 to 3 mol, per mol carboxylic acid amide.

The process of the invention is eligibly carried out in the presence of a solvent in which the aldehyde, the carboxylic acid amide, the catalyst and the cocatalyst are partially or completely soluble at the conditions of the reaction. The solvent may comprise a single solvent but it may also comprise a mixture of solvents, preferably a homogeneous mixture. In some instances the reactants, the carboxylic acid amide and/or the aldehyde, may be employed as the solvent. Suitable solvents are polar solvents, such as cyclic and acyclic esters, cyclic and acyclic ethers, carboxylic acids and tertiary amides. Examples of such solvents are ethylene carbonate, ethyl acetate, methyl propionate, dimethyl carbonate, tetrahydrofuran, 1,4-dioxane, glycol dimethyl ether, acetic acid and N,N-dimethylformamide. More preferred solvents are cyclic ethers and acyclic esters. Acyclic esters are especially preferred when an aldehyde according the general formula $R-CHO$ is used in which formula R represents an alkyl group. Very good results can be achieved with solvents comprising tetrahydrofuran, 1,4-dioxane, methyl acetate or dimethyl carbonate.

The temperature and pressure at which the process of the invention can be carried may vary widely. Preferably the process is carried out at a temperature of from 0 to 150 °C and at a carbon monoxide partial pressure of from 5 to 100 bar. More preferably the temperature is chosen between 50 and 100 °C and the carbon monoxide partial pressure is chosen between 10 and 80 bar.

In the process of the invention hydrogen or other diluent gases, such as nitrogen or helium, may be present in the carbon monoxide. Hydrogen may, for example, be present in a quantity of from 0.1 to 10 mol per mol of carbon monoxide. It is, however, a special and very advantageous feature of the process of the invention that - in contrast to the known processes - it can be

carried out substantially in the absence of hydrogen without an appreciable decrease of the reaction rate or the selectivity of the reaction. Also in case the aldehyde and/or the carboxylic acid amide are (is) prepared in situ as indicated hereinbefore, hydrogen
5 may be absent, obviously, provided that the in-situ preparation does not require the presence of hydrogen.

The process of the invention may be carried out batchwise or in a continuous mode of operation. The catalyst and the cocatalyst of the invention may be introduced simultaneously or separately,
10 either in the initial stage of the reaction or in the course of the reaction in a continuous or intermittent fashion. The N-acetyl- α -amino acid formed may be isolated from the reaction mixture by any known technique as the free acid or as a salt. Unconverted aldehyde and/or carboxylic acid amide and/or fractions
15 which are rich in the iron group metal originating from the catalyst may be recycled.

The invention will now be illustrated by the following non-limiting examples. In these examples the yield(s) of the desired product(s) was (were) determined by titration of carboxylic
20 acid obtained and calculated relatively to the intake of aldehyde, unless indicated otherwise. The reaction products have been identified by nuclear magnetic resonance. The average reaction rate is the rate of formation of the desired end-product(s) relative to the quantity of cobalt present in the reaction mixture
25 and has been calculated as an average over the reaction time.

Examples 1 - 13

N-Acetylglycine was prepared as follows. A magnetically stirred autoclave with a capacity of 250 ml was charged with

30 50 ml tetrahydrofuran,
90 mmol paraformaldehyde (the sample used contained, in addition, 10 %w water),
160 mmol acetamide,
variable quantities of dicobalt octacarbonyl ($\text{Co}_2(\text{CO})_8$), as
35 specified in Table I, and, optionally,

variable quantities of a cocatalyst, as specified in Table I. Air was removed from the autoclave by evacuation. The contents of the autoclave were heated to the reaction temperature, specified in Table I, and carbon monoxide was introduced to obtain a carbon
5 monoxide partial pressure of 60 bar. In examples 2, 3, and 8, hydrogen was introduced in addition to carbon monoxide to obtain a hydrogen partial pressure of 10, 10 and 20 bar, respectively. After elapse of the reaction time (Table I), the reaction was
10 terminated by cooling the autoclave and releasing the pressure. The results are given in Table I.

TABLE I

Example a)	Co ₂ (CO) ₈ mmol	Cocatalyst b) (mmol)	Temp. °C	Reaction time, hours	Yield %	Average reaction rate, mol/(mol Co.h)
1	1.0	-	90	10	trace ^{e)}	-
2 ^{c)}	1.0	-	90	8	70	4
3 ^{c)}	0.5	-	90	6	30 ^{e)}	5
4	1.0	PTSA (2.0)	90	0.25	60	110
5	1.0	BPA (2.0)	80	0.25	40	72
6	1.0	TFA (2.0)	75	0.5	75	68
7	0.25	TFSA (0.5)	75	0.5	82	295
8 ^{d)}	0.25	TFSA (0.5)	70	1	93	170
9	2.0	TFA (4.0)	60	2	93	21
10	1.0	HCl (2.0)	75	0.4	80	100
11	1.0	HCl (4.0)	75	0.25	100	200
12	1.0	TMBA (2.0)	90	5	15	about 2
13	1.0	TMBA (10)	90	6	30	about 2

a) no hydrogen present, unless indicated otherwise

b) PTSA: p-toluenesulphonic acid

BPA: benzenephosphonic acid

TFA: trifluoroacetic acid

TFSA: trifluoromethanesulphonic acid

HCl: hydrochloric acid (added as concentrated aqueous
hydrochloric acid)

TMBA: 2,4,6-trimethylbenzoic acid

c) hydrogen present (partial pressure 10 bar)

d) hydrogen present (partial pressure 20 bar)

e) a substantial quantity of N,N'-diacetyldiaminomethane had been
formed as well

Examples 14 - 17

N-Acetyl- α -aminopentanoic acid was prepared as follows. A magnetically stirred autoclave with a capacity of 250 ml was charged with

- 5 50 ml solvent, as specified in Table II,
 55 mmol butyraldehyde,
 85 mmol acetamide,
 1.0 mmol dicobalt octacarbonyl and, optionally,
 1.5 mmol of a cocatalyst, as specified in Table II.
- 10 Air was removed from the autoclave by evacuation. The contents of the autoclave were heated to 70 °C and carbon monoxide was introduced to obtain a carbon monoxide partial pressure of 60 bar. In example 17 hydrogen was introduced as well to obtain a hydrogen partial pressure of 20 bar. After elapse of the reaction time,
- 15 specified in Table II, the reaction was terminated by cooling the autoclave and releasing the pressure. The results are given in Table II.

TABLE II

Example a)	Cocatalyst b)	Solvent c)	Reaction time, hours	Yield %	Average reaction rate, mol/(mol Co.h)
14	PTSA	DMC	2.5	92	10
15	PTSA	MA	5	99	5
16	TFSA	1,4-dioxane	2.5	69	8
17 d)	-	DMC	15	trace	-

a) no hydrogen present, unless indicated otherwise

b) PTSA: p-toluenesulphonic acid
TFSA: trifluoromethanesulphonic acid

c) DMC: dimethyl carbonate
MA: methyl acetate

d) hydrogen present (partial pressure 10 bar)

Example 18

A mixture of N-Acetyl- α -aminodecanoic acid and N-acetyl- α -amino- β -methylnonanoic acid was prepared as follows. A magnetically stirred autoclave with a capacity of 250 ml was charged with

- 5 50 ml dimethyl carbonate,
 110 mmol octene-1,
 100 mmol acetamide,
 1.0 mmol dicobalt octacarbonyl and
 1.5 mmol p-toluenesulphonic acid.

- 10 Air was removed from the autoclave by evacuation. The contents of the autoclave were heated to 110 °C and carbon monoxide and hydrogen were introduced to obtain a carbon monoxide partial pressure of 40 bar and a hydrogen partial pressure of 20 bar. After 3 hours the reaction was terminated by cooling the autoclave
15 and releasing the pressure. The yield (based on the intake of octene-1) of N-acetyl- α -aminodecanoic acid was 65 %. The yield of N-acetyl- α -amino- β -methylnonanoic acid was 16 %. The average reaction rate was 14 mol/(mol cobalt.h).

- 20 Of Examples 1 - 18, the Examples 4 - 11, 14 - 16 and 18 are according to the invention. Examples 1 - 3, 12, 13 and 17 have been added for comparative purposes. No acid was added to the reaction mixtures of Examples 1 - 3 and 17. The acid added to the reaction mixtures of Examples 12 and 13 has a pKa of more than 3.

- 25 Examples 1 - 13 concern the preparation of N-acetyl-glycine from carbon monoxide, paraformaldehyde and acetamide. Examples 14 - 17 concern the preparation of N-acetyl- α -aminopentanoic acid from carbon monoxide, butyraldehyde and acetamide. Examples 18 concerns the preparation of a mixture of N-acetyl- α -aminodecanoic acid and N-acetyl- α -amino- β -methylnonanoic acid from carbon monoxide,
30 octene-1 and acetamide.

Comparison of Examples 4 - 11 with Examples 1 - 3, 12 and 13 teaches that the addition of a catalytic quantity of an acid with a pKa of less than 3 provides a substantial increase of the average rate of reaction without appreciable formation of by-products and

that the addition of a catalytic quantity of an acid with a pKa of more than 3 does not influence the rate of reaction to an appreciable extent. In particular trifluoromethanesulphonic acid has a large enhancing effect on the reaction rate. With respect to the influence of an acid with a pKa of less than 3, the same conclusion can be drawn from a comparison of Examples 14 - 16 with Example 17.

Comparison of Examples 1 and 2 shows that the process carried out in the absence of an acid with a pKa of less than 3 requires the presence of hydrogen, whereas Examples 4 - 7, 9 - 11 and 14 - 16 show that the process of the invention can be carried out in the absence of hydrogen. Comparison of Example 7 with Example 8 indicates that in the process of the invention there is no substantial influence of hydrogen on the rate of reaction. A skilled person will appreciate that the difference seen in the reaction rates in these Examples is mainly to be attributed to differences in the reaction temperature and to differences in the reaction times, the latter because at the end of the reaction times applied the conversion levels were such that paraformaldehyde approached exhaustion.

Examples 4 - 7 and 18 illustrate that in the process of the invention at least one of the reactants, i.e. the aldehyde and the carboxylic acid amide, can be prepared in situ. In Examples 4 - 7 formaldehyde was prepared in situ from paraformaldehyde, whereas in Example 18 a mixture of nonanal and 2-methyloctanal was prepared in situ from octene-1.

C L A I M S

- 5
1. A process for the preparation of N-acyl- α -amino acids by reacting carbon monoxide with an aldehyde and a carboxylic acid amide having an amide group with at least one hydrogen atom attached to the nitrogen atom which reaction is carried out in the presence of a catalyst, obtainable from a compound containing a metal selected from the iron group of the Periodic Table, and a cocatalyst which is an acid with a pKa of less than 3 added in a quantity of less than 0.1 mol per mol of the carboxylic acid amide.
- 10
2. A process as claimed in claim 1, characterised in that the cocatalyst is an acid with a pKa of less than 2.
3. A process as claimed in claim 2, characterised in that the cocatalyst is an acid selected from the group consisting of sulphonic acids, carboxylic acids, phosphonic acids and hydrohalogenic acids.
- 15
4. A process as claimed in claim 3, characterised in that the cocatalyst is an acid selected from the group consisting of trifluoromethanesulphonic acid, p-toluenesulphonic acid, trifluoroacetic acid, benzenephosphonic acid and hydrochloric acid.
- 20
5. A process as claimed in claim 3, characterised in that the cocatalyst is a (perfluoro-n-alkyl)sulphonic acid.
6. A process as claimed in claim 5, characterised in that the cocatalyst is trifluoromethanesulphonic acid.
7. A process as claimed in any of claims 1 - 6, characterised in that the cocatalyst is added in a quantity of from 0.0001 to
- 25
0.05 mol per mol of the carboxylic acid amide.
8. A process as claimed in claim 7, characterised in that the cocatalyst is added in a quantity of from 0.001 to 0.03 mol per mol of the carboxylic acid amide.

9. A process as claimed in any of claims 1 - 8, characterised in that the cocatalyst is added in a quantity of from 0.1 to 2 mol per gram atom of iron group metal.
10. A process as claimed in claim 9, characterised in that the
5 cocatalyst is added in a quantity of from 0.5 to 1 mol per gram atom of iron group metal.
11. A process as claimed in any of claims 1 - 10, characterised in that the metal selected from the iron group is cobalt.
12. A process as claimed in any of claims 1 - 11, characterised in
10 that the compound containing a metal selected from the iron group is a cobalt carbonyl.
13. A process as claimed in claim 12, characterised in that the cobalt carbonyl is dicobalt octacarbonyl.
14. A process as claimed in any of claims 1 - 13, characterised in
15 that the catalyst is present in such a quantity as to contain from 0.001 - 0.03 gram atom iron group metal per mol of the carboxylic acid amide.
15. A process as claimed in any of claims 1 - 14, characterised in that the aldehyde is of the general formula $R-CHO$ wherein R
20 represents hydrogen or an alkyl group.
16. A process as claimed in any of claims 1 - 15, characterised in that the carboxylic acid amide is of the general formula $R^1-CO-NH_2$, wherein R^1 represents an alkyl group.
17. A process as claimed in any of claims 1 - 16, characterised in
25 that the aldehyde is used in a quantity of from 0.3 to 3 mol per mol of the carboxylic acid amide.
18. A process as claimed in any of claims 1 - 17, characterised in that it is carried out in the presence of a solvent selected from the group consisting of esters and cyclic ethers.
19. A process as claimed in any of claims 1 - 18, characterised in
30 that it is carried out at a temperature of from 50 to 100 °C and at a carbon monoxide partial pressure of from 10 to 80 bar.
20. A process as claimed in any of claims 1 - 19, characterised in that it is carried out substantially in the absence of hydrogen.

21. A process as claimed in claim 1 and substantially as
hereinbefore described with particular reference to Examples 4 -
11, 14 - 16 and 18.

22. N-acyl- α -amino acid obtained by a process as claimed in any of
5 claims 1 - 21.

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Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: CAS-ON-LINE

Search Examiner

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Documents considered relevant following a search in respect of claims

1-22

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
	NONE	

SF2(p)

sf - c:\wp51\doc99\fil002038

Category	Identity of document and relevant passages	Relevant to claim(s)

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